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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,296	BRUNE ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,21 and 24-38* is/are pending in the application.

4a) Of the above claim(s) *21,28 and 31-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,24-27,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1&5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

Claims 20, 21, and 24-38 are pending in the application.

Applicants' election with traverse of Group I, claims 20, 24-27, 29, and 30, amendment to claims 20, 21, 24, and 31, and cancellation of claims 22 and 23 in Paper No. 7, filed 08/26/02 is acknowledged.

Lack of Unity

1. Applicants traverse the lack of unity on the grounds that claims 20, 21, and 31 have been amended to recite the same special technical feature and that the claims as amended are not anticipated by Biondi et al. While applicants' amendment to claim 31 is sufficient to obviate anticipation by Biondi et al., the NDPK of claim 31 was known in the art at the time of the invention. For example, Schneider et al. (J Biol Chem 273:11491-11497) teach a *Dictyostelium discoideum* NDPK modified to replace phenylalanine with tryptophan at position 64 (page 11492, left column). Schneider et al. teach the fluorescence signal, which is correlated with the phosphorylation state of the enzyme, decreases upon ddNTP addition due to quenching of tryptophan fluorescence (page 11491 and page 11494, Fig 3). Schneider teaches the mutant NDPK has essentially the same kinetic and binding constants as the wild-type enzyme (Table II, page 11495) and the intrinsic fluorescence of the mutant protein is primarily due to tryptophans at positions 64 and 137 (page 11495, left column). In summary, the NDPK of Schneider et al. has been modified by site-directed mutagenesis to carry an additional tryptophan residue that is present in both the phosphorylated and unphosphorylated forms, and wherein the fluorescence of the tryptophan residues at positions 64 and 137 changes due to the phosphorylation state of the enzyme. Also, the invention of Group I was obvious as described below. Thus, the inventions of Groups I-III as set forth in Paper No. 6, when considered as a whole, do not contribute over the prior art.

The requirement is still deemed proper and is therefore made FINAL.

Claims 21, 28, and 31-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Specification/Informalities

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Assay for Nucleoside Diphosphate Using a Modified Nucleoside Diphosphate Kinase Comprising a Fluorescent Label". See MPEP § 606.01.

Claim Objections

3. Claims 24, 29 and 30 are objected to as being dependent upon non-elected claims. It is suggested that applicants amend the dependency of the claims to reflect the elected invention of Group I.

4. Claim 30 is objected to in the recitation of "carrying an IDCC label at this mutated residue". In the interest of clarity, it is suggested that the term be replaced with, for example, "carrying an IDCC label attached to this mutated residue".

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 20, 24-27, 29, and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 20 (claims 24-27, 29, and 30 dependent therefrom) is confusing in the recitation of "NDPK is modified to carry a label in both its phosphorylated and unphosphorylated forms". It is unclear from the claims as to whether the term "phosphorylated and unphosphorylated forms" is meant to refer to "phosphorylated and unphosphorylated forms" of an NDPK or "phosphorylated

and unphosphorylated forms" of a label. It is suggested that applicants clarify the claim by replacing the term "NDPK is modified to carry a label in both its phosphorylated and unphosphorylated forms" with, for example, "NDPK is modified to carry a label in both the NDPK's phosphorylated and unphosphorylated forms".

b. Claim 30 recites the limitation "the NDPK of *Myxococcus*". There is insufficient antecedent basis for this limitation in the claim. It is suggested that applicants replace the term with, for example, "an NDPK of *Myxococcus*".

c. Claim 30 is indefinite in the recitation of "*Myxococcus xanthus* carrying a Asp112→Cys mutation". The claim is indefinite because applicant has not provided the amino acid sequence of the *Myxococcus xanthus* enzyme necessary for one to determine the position of the mutant NDPK as recited in the claim and therefore, to define the metes and bounds of the claims. The incorporation of this essential material by merely providing descriptions of the terms, i.e., "*Myxococcus xanthus* NDPK" and "Asp112→Cys" in the claims and specification and a reference disclosing the sequence of *Myxococcus xanthus* NDPK (page 7 of the instant specification) are improper. Applicant should provide a sequence of the *Myxococcus xanthus* NDPK enzyme to which the terms refer. Applicant should refer to MPEP section 2420 for the requirements for patent applications containing amino acid sequences.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 20, 24-27, and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 20 (claims 27 and 29 dependent therefrom) is drawn to a process for detecting the presence of a nucleoside diphosphate in a sample, comprising a step of detecting the dephosphorylation of the phosphoenzyme form of a genus of modified NDPKs that carry a genus of labels in both its phosphorylated and unphosphorylated forms, wherein the label gives a different detectable signal when the enzyme is phosphorylated from when it is not. Claims 24-26 limit the label carried by the NDPK. The specification teaches the structure of only a single representative species of such modified NDPKs, i.e., *Myxococcus xanthus* NDPK with aspartate at position 112 replaced with cysteine carrying an IDCC label. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being a modified NDPK that carries a label in both its phosphorylated and unphosphorylated forms, wherein the label gives a different detectable signal when the enzyme is phosphorylated from when it is not. It is noted that applicants have provided the disclosure of *Myxococcus xanthus* NDPK with aspartate at position 62 replaced with cysteine (page 8, line 15 of the specification), however, it is unclear from the specification as to whether this mutant can be used for the recited method. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

7. Claims 20, 24-27, and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for detecting the presence of a nucleoside diphosphate in a sample, comprising a step of detecting the dephosphorylation of the phosphoenzyme form of *Myxococcus xanthus* NDPK with aspartate at position 112 replaced with cysteine carrying an IDCC label by monitoring a change in fluorescence due to dephosphorylation of the enzyme, does not reasonably provide enablement for a process for detecting the presence of a nucleoside diphosphate in a sample, comprising a step of detecting the dephosphorylation of the phosphoenzyme form of *any* NDPK with *any*

modification to carry *any* label, *any* fluorescent label (and optionally wherein the label is attached via a cysteine residue), or IDCC in both its phosphorylated and unphosphorylated forms, wherein the label gives a different detectable signal when the enzyme is phosphorylated from when it is not. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 20 (claims 27 and 29 dependent therefrom) and 24-26 are so broad as to encompass a process using *any* NDPK modified by *any* method to carry *any* of the labels described above. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of modified NDPK enzymes and detectable labels broadly encompassed by the claims. The specification provides only a single example of an NDPK modified as recited in claim 20, i.e., *Myxococcus xanthus* NDPK with aspartate at position 112 replaced with cysteine carrying an IDCC label. It is noted that the specification suggests mutating *Myxococcus xanthus* NDPK with aspartate at position 62 to a cysteine (page 8, line 15 of the specification), however, it is unclear from the specification as to whether this mutant can be used for the recited method. Such modifications, e.g., amino acid substitutions that result in the incorporation of a detectable label are unpredictable and may result in loss of function of the enzyme. For example, regarding claim 25, not all NDPK proteins have a cysteine residue (see for example Izymiya et al. *J Biol Chem* 270:27859-27864) and therefore, a cysteine residue must be incorporated to carry a fluorescent label, e.g., IDCC. One of skill in the art would recognize that such modifications to incorporate labels detectable by methods such as fluorescence typically must be near the active site/ligand binding site of an enzyme and thus the result of such modification on the

function of the enzyme is highly unpredictable. Since a modification to an amino acid sequence of a protein can affect the functional properties of the enzyme, predictability of which changes can be tolerated in a protein's amino acid sequence and without abolishing biological activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a process for detecting the presence of a nucleoside diphosphate in a sample, comprising a step of detecting the dephosphorylation of the phosphoenzyme form of *Myxococcus xanthus* NDPK with aspartate at position 112 replaced with cysteine carrying an IDCC label by monitoring a change in fluorescence due to dephosphorylation of the enzyme. While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for an enzyme for use in a particular process having multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass a process using *any* NDPK modified by *any* method to carry *any* of the labels described above because the specification does not establish: (A) guidance as to the combination of NDPKs, modifications thereto, and labels which are likely to be successful in practicing the claimed process; (B) the general tolerance of *all* NDPKs to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying *any* NDPK by any method to carry a label as encompassed by the claims with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a process using *any* NDPK modified by *any* method to carry *any* of the labels described above. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re* Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 20, 24, 27, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider et al. (J Biol Chem 273:11491-11497, 1998; hereafter referred to as "Schneider") in view of Deville-Bonne et al. (Biochemistry 35:14643-14650, 1996; hereafter referred to as "Deville-Bonne". Claim 20 is drawn to a process for detecting the presence of a nucleoside diphosphate in a sample, comprising a step of detecting the dephosphorylation of the phosphoenzyme form of a modified NDPK that carries a label in both its phosphorylated and unphosphorylated forms, wherein the label gives a different detectable signal when the enzyme is phosphorylated from when it is not. Claim 24 limits the label of claim 20 to a fluorescent label. Claim 27 limits the nucleoside diphosphate of claim 20 to ADP or GDP. Claim 29 limits claim 20 to a quantitative process.

Schneider teaches a *Dictyostelium discoideum* NDPK modified to replace phenylalanine with tryptophan at position 64 (page 11492, left column). Schneider teaches the fluorescence signal of the

enzyme is correlated with the phosphorylation state of the enzyme (page 11491 and page 11494, Fig 3). Schneider teaches the mutant NDPK has essentially the same kinetic and binding constants as the wild-type enzyme (Table II, page 11495) and the intrinsic fluorescence of the mutant protein is primarily due to tryptophans at positions 64 and 137 (page 11495, left column).

Deville-Bonne teaches *Dictyostelium discoideum* NDPK has a single tryptophan residue at position 137 that can be used as a probe for monitoring intrinsic fluorescence (page 14643, abstract). Deville-Bonne teaches the dephosphorylation of the phosphorylated NDPK intermediate as monitored by fluorescence as a function of increasing amounts of ADP (page 14647, Figure 4). Deville-Bonne teaches that fluorescence of the single tryptophan residue at position 137 of *Dictyostelium discoideum* NDPK is strongly quenched by a histidine at residue 55 (page 14648, right column and page 14646, Figure 1).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Schneider and Deville-Bonne to use a *Dictyostelium discoideum* NDPK with a phenylalanine to tryptophan mutation at position 64 for monitoring the fluorescence of the dephosphorylation of the phosphorylated intermediate due to the addition of ADP. One would have been motivated to use a *Dictyostelium discoideum* NDPK with an additional tryptophan to monitor fluorescence in the presence of increasing amounts of ADP in order to increase the signal (intrinsic fluorescence) of the reaction because of the quenching of the single tryptophan of the wild-type enzyme as described above. One would have a reasonable expectation of success for using a *Dictyostelium discoideum* NDPK with a phenylalanine to tryptophan mutation at position 64 to monitor the dephosphorylation of the phosphorylated intermediate in the presence of increasing amounts of ADP because of the results of Schneider and Deville-Bonne. Therefore, claims 20, 24, 27, and 29, drawn to a process for detecting nucleoside diphosphates as described above would have been obvious to one of ordinary skill in the art.

Conclusion

9. All claims are rejected. No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:30 am to 2:00 pm and from 3:30 pm to 5:30 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.

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